(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

B2

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/087399 A1

(51) International Patent Classification[7]: C12Q 1/26, A61K 31/03, 31/12, A61P 3/10

(21) International Application Number: PCT/SE03/00618

(22) International Filing Date: 16 April 2003 (16.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0201152-6 17 April 2002 (17.04.2002) SE
60/410,626 13 September 2002 (13.09.2002) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/087399 A1

(54) Title: NAD)P)H OXIDASE INHIBITORS FOR INCREASED GLUCOSE UPTAKE AND TREATMENT OF TYPE II DIABETES

(57) Abstract: The present invention relates to the use of NAD(P)H oxidase inhibitors to increase cellular uptake of glucose and in the treatment and/or prevention of diseases caused by insulin resistance or diseases related thereto, such as type II diabetes. Specifically, the invention relates to a method for identifying an agent useful for the treatment or prophylaxis of a medical condition associated with elevated levels of blood glucose, the method comprising (i) contacting a candidate agent with a mammalian NAD(P)H oxidase or NAD(P)H oxidase complex; and (ii) determining whether said candidate agent inhibits the biological activities of the NAD(P)H oxidase or NAD(P)H oxidase complex.

NAD(P)H Oxidase inhibitors for increased glucose uptake and treatment of type II diabetes.

TECHNICAL FIELD

The present invention relates to the use of NAD(P)H oxidase inhibitors to increase cellular uptake of glucose and in the treatment and/or prevention of diseases caused by insulin resistance or diseases related thereto, such as type II diabetes.

BACKGROUND ART

A large number of people suffer, or are predisposed to suffer from disturbances in their metabolism. One such disturbance includes insulin resistance, which is characteristic of the metabolic syndrome (syndrome X), polycystic ovary syndrome, obesity and type II diabetes, diseases that are rapidly growing in number in the western world. These diseases are multi-factorial and their mechanism or physiology are, in the majority of cases, not well characterized or understood. Type II diabetes includes the most prevalent form of diabetes, which results from insulin resistance with an insulin secretory defect. Pharmacological treatments such as metformin and rosiglitazone have an ameliorating effect on insulin resistance and are believed to increase the effectiveness of endogenous insulin and thereby contribute to the lowering of elevated blood glucose levels in type II diabetes patients.

One mechanism whereby insulin resistance may be induced is via elevation of reactive oxygen species (ROS). Although contrasting effects of ROS have been reported on the insulin signal transduction system and glucose transport, it has been shown that prolonged exposure of cells to ROS causes insulin resistance. Insulinomimetic effects of ROS have been reported using muscle cells and adipocytes. Acute exposure of adipocytes to H_2O_2 was shown to activate pyruvate dehydrogenase activity and lipid synthesis [May et al., Journal of Biological Chemistry, 254:9017-21 (1979)]. Some but not all aspects of insulin signaling appear to be activated by H_2O_2. Using L6 myocytes it was shown that H_2O_2 caused a PI3K-dependent activation of PKB and inhibition of GSK3 within 30 min of treatment [Tirosh et al., Journal of Biological Chemistry, 274:10595-602 (1999)]. Prolonged treatment (24 h) of L6 muscle cells and 3T3-L1 adipocytes with a ROS generating system increased the expression of GLUT1 that resulted in elevated basal glucose transport [Kozlovsky et al., Free Radical Biology & Medicine, 23:859-69 (1997); Kozlovsky et al., Journal of Biological Chemistry,

272:33367-72 (1997)]. Treatment of these cell lines with H_2O_2 also interferes with insulin signaling [Rudich et al., American Journal of Physiology, 272:E935-40 (1997)]. Simultaneous treatment with insulin and H_2O_2 was shown to inhibit insulin stimulated glucose transport and glycogen synthesis in spite of intact PKB activation [Blair et al., Journal of Biological Chemistry, 274:36293-9 (1999)]. Pretreatment with ROS inhibited insulin stimulated IRS-1 and PI3K cellular redistribution, PKB serine phosphorylation and glucose transport [Tirosh, Potashnik et al., Journal of Biological Chemistry, 274:10595-602 (1999)]. The antioxidant lipoic acid could prevent these effects [Rudich et al., Diabetologia, 42:949-57 (1999)]. Taken together, these results suggest that insulin signaling involve redox reactions, with some steps that can be mimicked and some that can be inhibited by H_2O_2. Integrating these findings with the demonstration that insulin can stimulate the production of H_2O_2, it can be hypothesized that ROS are involved in insulin signaling and may be responsible for the insulin resistance observed after prolonged treatment with insulin and other agents.

Oxidative stress is caused by excess free radical production in cellular metabolism. The free radicals derived from reaction products of oxygen are often termed reactive oxygen species (ROS). A reducing environment inside the cell prevents oxidative damage and can be maintained by the action of antioxidant enzymes and substances, such as superoxide dismutase (SOD), catalase, glutathione, selenium-dependent glutathione, thioredoxin hydroperoxidases, thioredoxin, vitamins C and E, and probably more unknown players.

Oxidative stress has been demonstrated in several different diseases and is implicated as an important driving force in the aging process [Finkel et al., Nature, 408:239-47 (2000); Spector, Journal of Ocular Pharmacology & Therapeutics, 16:193-201 (2000)]. A growing body of data demonstrate signs of increased oxidative stress in type II diabetes. It is likely that the oxidative stress is contributing to many of the vascular complications occurring in the late stages of the disease but the evidence for oxidative stress as causative factor in the development of insulin resistance and deterioration of beta cell function is still lacking. An inverse relationship between insulin action on glucose disposal and plasma superoxide ion, and a positive relationship between insulin action on glucose disposal and plasma GSH/GSSG ratio have been observed in type 2 diabetic patients during euglycemic hyperinsulinemic clamp [Paolisso et al., Metabolism: Clinical & Experimental, 43:1426-9 (1994)]. Decreased serum vitamin E content, a marker of impaired oxidant/antioxidant status,

was reported to be associated with increased risk of developing type II diabetes [Salonen et al., BMJ, 311:1124-7 (1995)]. In animal experiments it was recently demonstrated that chemically induced oxidative stress exacerbated insulin resistance and hyperglycemia in obese Zucker rats [Laight et al., British Journal of Pharmacology, 128:269-71 (1999)]. There are also indications that beta cell toxic agents like alloxan and streptozotocin that are used to induce experimental animal diabetes act via oxidative stress [Davis et al., Biochemical Pharmacology, 55:1301-7 (1998); Hotta et al., Journal of Experimental Medicine, 188:1445-51 (1998)].

Superoxide can be produced by a number of cellular enzyme systems: NAD(P)H oxidases, xanthine oxidase, lipoxygenases, cyclooxygenase, P-450 monooxygenases, and the enzymes of mitochondrial oxidative phosphorylation. The majority of free radicals are produced by the mitochondria as unwanted by-products of the respiratory chain but the cell also purposely generates free radicals. The cellular defense system of the body utilizes oxygen radicals to kill invading microorganisms and the vascular system uses the nitric oxide radicals as an intermediate in the regulation of vascular tone. Originally, the NAD(P)H oxidase system responsible for production of superoxide that participates in bacterial killing was demonstrated in neutrophils and other phagocyte cells [Segal et al., Annals of the New York Academy of Sciences, 832:215-22 (1997)]. A growing number of experimental data from endothelial cells and other cell types show that ROS can be produced through activation of NAD(P)H-oxidase [Jones et al., American Journal of Physiology, 271:H1626-34 (1996); Krieger-Brauer et al., Journal of Biological Chemistry, 272:10135-43 (1997); Bayraktutan et al., Cardiovascular Research, 38:256-62 (1998)]. When activated, the NAD(P)H oxidase assembles at the plasma membrane and catalyses the single electron reduction of molecular O_2 to superoxide (O_2^-). In the presence of superoxide dismutase, O_2^- dismutates to hydrogen peroxide (H_2O_2) that can be converted to a hydroxyl radical (OH^-) in the presence of ferrous ions. The list of other free radicals originating from O_2^- that can be formed in the cell is longer, and will not be further discussed here. At least five proteins are required for the formation of an active NAD(P)H oxidase complex: the membrane bound cytochrome b558 and the cytosolic proteins, $p47^{phox}$, $p67^{phox}$, $p40^{phox}$ and a small GTP-binding protein, Rac-1 or Rac-2 [Abo et al., Journal of Biological Chemistry, 267:16767-70 (1992); Babior, Advances in Enzymology & Related Areas of Molecular Biology, 65:49-95 (1992); Knaus et al., Journal of Biological Chemistry, 267:23575-82 (1992)]. Cytochrome b558 is a flavoprotein with an NAD(P)H-binding

site and consists of two subunits, gp91 ^{phox} and p22 ^{phox} [Sumimoto et al., Biochemical & Biophysical Research Communications, 186:1368-75 (1992)].

The hypoglycemic agent diphenylene iodinium (DPI) has been shown to diminish the rate of mitochondrial respiration by inhibiting NADH dehydrogenase. Holland et al. (1973; J. Biol. Chem. 248: 6050-6056) discloses that the enzyme inhibition causes the hypoglycemic action by decreasing mitochondrial oxidation and the hepatic and whole body ATP content (See also Gatley, S.J. & Martin, J.L. (1979) Xenobiotica 9: 539-546). However, it has not been previously shown that agents which inhibit NAD(P)H oxidase would be useful for increasing the activity of the insulin receptor and/or the intracellular insulin-signaling pathway, and thereby be useful against insulin resistance.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig.1 is a graph depicting the effect of DPI on insulin stimulated glucose transport in L6 cells when treated with different concentrations (0.1–10 μM) of DPI alone for 30 min or together with insulin (200 or 1000 nM) for additional 30 min.

Fig. 2 is a graph depicting the effect of H_2O_2 generated by glucose oxidase (GO) DPI stimulated glucose transport. Differentiated L6 cells were treated with 25 mU/ml GO for 30 min before addition of DPI. After additional 30 min, 200 nM insulin was added and glucose transport was measured after 30 min.

Fig. 3 is a graph depicting blood glucose concentrations during an insulin tolerance test in ob/ob mice treated for 4 days with daily i.p. injections of DPI, 1 mg/kg (n=7), or vehicle (n=8).

DISCLOSURE OF THE INVENTION

It has surprisingly been found that inhibition of NAD(P)H oxidase stimulates glucose uptake in rat skeletal muscle cells. A NAD(P)H oxidase complex is putatively involved in down-regulation of insulin signaling via generation of ROS. Thus, pharmacological inhibition of NAD(P)H oxidase activity should increase insulin signaling and restore insulin sensitivity. This surprising effect has not been seen previously and demonstrates the utility of the entire, or parts of, NAD(P)H oxidase complex, which generates ROS, as a tool for finding drugs that can be used for treating type II diabetes, specifically insulin resistance.

Consequently, in a first aspect this invention provides a method for identifying an agent useful for the treatment or prophylaxis of a medical condition associated with elevated levels of blood glucose, said method comprising

(i) contacting a candidate agent with a mammalian NAD(P)H oxidase or NAD(P)H oxidase complex; and

(ii) determining whether said candidate agent inhibits the biological activities of the NAD(P)H oxidase or NAD(P)H oxidase complex.

The said medical condition is preferably associated with insulin resistance, such as, in particular, type II diabetes. One clinical definition of diabetes is the so-called fasting glucose level. A patient is diagnosed with diabetes if the amount of glucose is above 126 milligrams per deciliter (mg/dl) measured on two occasions. Impaired fasting glucose and impaired glucose tolerance are associated with the insulin resistance syndrome. An individual can be insulin resistant in the absence of fasting hyperglycemia if an oral glucose tolerance test with 75 g anhydrous glucose dissolved in water gives a 2 h plasma glucose value $\geq$200 mg/dl in a test performed as described by WHO [World Health Organization, Tech. Rep. Ser., no. 727, (1985)].

In one embodiment of the invention, cells containing the NAD(P)H oxidase or the NAD(P)H oxidase complex may be brought into contact with inhibitors of the NAD(P)H oxidase or the NAD(P)H oxidase complex, followed by monitoring the glucose uptake by these cells, and comparing this activity with that of a the NAD(P)H oxidase or the NAD(P)H oxidase complex in the absence of inhibitor. Compounds that affect the glucose uptake of these cells are to be considered as potential drug candidates.

The NAD(P)H oxidase or NAD(P)H oxidase complex is preferably selected from the group consisting of gp91phox, p22phox, Mox2, Nox4, Nox5, DUOX1, DUOX2, (b5+b5R) oxidoreductase, p47phox, p67phox, p40phox, Rac-1, and Rac-2.

The proteins may be of any mammalian species, however, a preferred species is *Homo sapiens*. The nucleotide and amino acid sequences from *Homo sapiens* are disclosed in the enclosed sequence listing.

In one embodiment, the invention includes a method for identifying an agent that increases glucose uptake by a cell. The method includes the following steps: contacting a cell with a candidate agent that inhibits the activity of an NAD(P)H oxidase or an NAD(P)H oxidase complex; measuring glucose uptake by the cell in the presence of the candidate agent; and determining whether the candidate agent increases glucose uptake by the cell.

The method can optionally include an additional step of comparing glucose uptake by the cell in the presence of the candidate agent with glucose uptake by a cell in the absence of the candidate agent.

The method can optionally include a step of contacting the candidate agent with the NAD(P)H oxidase or the NAD(P)H oxidase complex and determining that the candidate agent inhibits the activity of the NAD(P)H oxidase or the NAD(P)H oxidase complex.

In one example, the NAD(P)H oxidase or the NAD(P)H oxidase complex is a human NAD(P)H oxidase or a human NAD(P)H oxidase complex. The NAD(P)H oxidase or the NAD(P)H oxidase complex can optionally be selected from the group consisting of gp91phox, p22phox, Mox2, Nox4, Nox5, DUOX1, DUOX2, (b5+b5R) oxidoreductase, p47phox, p67phox, p40phox, Rac-1, and Rac-2. The nucleic acid and amino acid sequences of exemplary NAD(P)H oxidases and NAD(P)H oxidase complexes are described herein.

The cell can be, for example, a muscle cell or an adipocyte.

In some embodiments, the candidate agent is selected from the group consisting of pyridine, imidazole, diethyl pyrocarbonate, chloromercuribenzoic acid, 4-(2-aminomethyl)-sulfonyl fluoride acetovanillone, and derivatives thereof.

In another aspect, the invention features a method for increasing glucose uptake in a cell by contacting a cell with an amount of an inhibitor of an NAD(P)H oxidase or an NAD(P)H oxidase complex effective to increase glucose uptake by the cell. The cell can be, for example, a muscle cell or an adipocyte. The method can optionally include an additional step of detecting an increase in glucose uptake by the cell in response to the contacting of the cell with the inhibitor.

In one example, the NAD(P)H oxidase or the NAD(P)H oxidase complex is a human NAD(P)H oxidase or a human NAD(P)H oxidase complex. The NAD(P)H oxidase or the NAD(P)H oxidase complex can optionally be selected from the group consisting of gp91phox, p22phox, Mox2, Nox4, Nox5, DUOX1, DUOX2, (b5+b5R) oxidoreductase, p47phox, p67phox, p40phox, Rac-1, and Rac-2. The nucleic acid and amino acid sequences of exemplary NAD(P)H oxidases and NAD(P)H oxidase complexes are described herein.

In some embodiments, the inhibitor is selected from the group consisting of pyridine, imidazole, diethyl pyrocarbonate, chloromercuribenzoic acid, 4-(2-aminomethyl)-sulfonyl fluoride acetovanillone, and derivatives thereof.

In another aspect, the invention provides a method for the treatment of a medical condition associated with elevated levels of blood glucose, comprising administering to a patient in need thereof an effective amount of an inhibitor or antagonist of NAD(P)H oxidase or NAD(P)H oxidase complex.

In one embodiment, the invention features a method for the treatment of a medical condition, including the following steps: selecting an individual diagnosed as having a medical condition characterized by elevated levels of blood glucose; and administering to the individual an amount of an inhibitor of an NAD(P)H oxidase or an NAD(P)H oxidase complex effective to reduce blood glucose levels in the individual.

The medical condition can be characterized by, for example, insulin resistance, a need for increased activity of the insulin receptor, and/or a need for increased activity of the intracellular insulin-signaling pathway.

In one example, the medical condition is diabetes, e.g., type II diabetes.

In some embodiments, the individual does not have and/or has not been diagnosed as having a disorder (e.g., atherosclerosis) characterized by a vascular injury, e.g., vascular hyperpermeability of endothelial cells. In addition, in some embodiments, the method does not include a step of evaluating a vascular injury (if present) in the individual before and/or after the administration of the inhibitor to the individual.

In some embodiments, the method includes an additional step of detecting a reduction in blood glucose levels in the individual in response to the administration of the inhibitor.

In one example, the NAD(P)H oxidase or the NAD(P)H oxidase complex is a human NAD(P)H oxidase or a human NAD(P)H oxidase complex. The NAD(P)H oxidase or the NAD(P)H oxidase complex can optionally be selected from the group consisting of gp91phox, p22phox, Mox2, Nox4, Nox5, DUOX1, DUOX2, (b5+b5R) oxidoreductase, p47phox, p67phox, p40phox, Rac-1, and Rac-2. The nucleic acid and amino acid sequences of exemplary NAD(P)H oxidases and NAD(P)H oxidase complexes are described herein.

In some embodiments, the inhibitor is selected from the group consisting of pyridine, imidazole, diethyl pyrocarbonate, chloromercuribenzoic acid, 4-(2-aminomethyl)-sulfonyl fluoride acetovanillone, and derivatives thereof.

The inhibitor or antagonist can be identified according to the method as described above. Examples of known inhibitors or antagonists are those selected from the group consisting of pyridine, imidazole, diethyl pyrocarbonate,

chloromercuribenzoic acid, 4-(2-aminomethyl)-sulfonyl fluoride and acetovanillone, including derivatives thereof. The said inhibitor or antagonist is e.g. a compound having an inhibitory effect on the ROS generating activity of the NAD(P)H oxidase or the NAD(P)H oxidase complex. The inhibitor or antagonist could exert its effect by interacting with the active site or a regulatory site, or both sites, of the NAD(P)H oxidase.

A compound that shows the desirable characteristics with regards to inhibiting the activity of the NAD(P)H oxidase or the NAD(P)H oxidase complex will be further tested in an assay of insulin stimulated glucose uptake in differentiated L6-K1 cells or other skeletal muscle cells, muscle tissue biopsies, adipocytes or adipocyte cell lines. An active compound should stimulate basal and insulin stimulated glucose uptake in a manner similar to the NAD(P)H oxidase inhibitor diphenylene iodonium (DPI). The compounds will preferably be of such nature that they are suited for oral administration, but any route of administration, such as, intravenous, suppository or parental routes will be considered.

In yet another aspect, the invention provides the use of an NAD(P)H oxidase- or NAD(P)H oxidase complex inhibitor or antagonist, as described above, in the manufacture of a medicament for the treatment and/or prevention of a medical condition connected with elevated levels of blood glucose.

As defined herein, the term "prevent" or "treat" is not intended to exclusively mean the complete abolishment of the disease or condition, but is meant that there is complete or some amelioration, so that an improvement over the expected symptomology is clinically observed. An example of one such criterion could be the lowering of blood glucose levels by more than 25%. Other such criteria, well known in the art, could be envisioned.

As defined herein, the term "reactive oxygen species" means compounds selected from the group comprising compounds or compound species such as H_2O_2, OH^- and O_2^-. Compounds such as these will be referred to as "ROS".

As defined herein, the term "NAD(P)H oxidase" or "NAD(P)H oxidase complex" means one of the proteins or any combination of two or more of the proteins selected from the group comprising the membrane bound cytochrome b558 consisting of $gp91^{phox}$ (nucleotide sequence according to SEQ ID NO:1, amino acid sequence according to SEQ ID NO:2), $p22^{phox}$ (nucleotide sequence according to SEQ ID NO:3, amino acid sequence according to SEQ ID NO:4), Mox2 (nucleotide sequence

according to SEQ ID NO:5, amino acid sequence according to SEQ ID NO:6), Nox4 (nucleotide sequence according to SEQ ID NO:7, amino acid sequence according to SEQ ID NO:8), Nox5 (nucleotide sequence according to SEQ ID NO:9, amino acid sequence according to SEQ ID NO:10), DUOX1 (nucleotide sequence according to SEQ ID NO:11, amino acid sequence according to SEQ ID NO:12), p138Tox (DUOX2) (nucleotide sequence according to SEQ ID NO:13, amino acid sequence according to SEQ ID NO:14), (b5+b5R) oxidoreductase (nucleotide sequence according to SEQ ID NO:15, amino acid sequence according to SEQ ID NO:16), and the cytosolic proteins, $p47^{phox}$ (nucleotide sequence according to SEQ ID NO:17, amino acid sequence according to SEQ ID NO:18), $p67^{phox}$ (nucleotide sequence according to SEQ ID NO:19, amino acid sequence according to SEQ ID NO:20), $p40^{phox}$ (nucleotide sequence according to SEQ ID NO:21, amino acid sequence according to SEQ ID NO:22),and a small GTP-binding protein, Rac-1, (which has two different amino acid variants), (nucleotide sequence according to SEQ ID NO:23, amino acid sequence according to SEQ ID NO:24 and SEQ ID NO:25, respectively), or Rac-2, (nucleotide sequence according to SEQ ID NO:26, amino acid sequence according to SEQ ID NO:27), which combination gives rise to reactive oxygen species, or other proteins or assemblies of proteins which essentially have NAD(P)H oxidase activity. Preferably, these enzymes contain consensus sequences for FAD- and/or NAD(P)H-binding sites.

In addition to the specific NAD(P)H oxidase amino acid and nucleotide sequences described herein, fragments or variants thereof that retain NAD(P)H oxidase activity (or fragments or variants thereof that encode polypeptides that retain such activity) can be used in the methods of the invention (e.g., screening methods).

In some embodiments, a polypeptide used in a method of the invention differs from an NAD(P)H oxidase amino acid sequence described herein at one or more residues and yet retains NAD(P)H oxidase activity. The differences are, preferably, differences or changes at a non-essential residue or a conservative substitution. In one embodiment, a polypeptide includes an amino acid sequence that is at least about 60% identical to an NAD(P)H oxidase amino acid sequence described herein or a fragment thereof. Preferably, the polypeptide is at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% or more identical to an NAD(P)H oxidase amino acid sequence described herein. Preferred polypeptide fragments are at least 10%, preferably at least 20%, 30%, 40%, 50%, 60%, 70%, or more, of the length of an NAD(P)H oxidase amino acid sequence described herein.

As used herein, "% identity" of two amino acid sequences, or of two nucleic acid sequences, is determined using the algorithm of Karlin and Altschul (PNAS USA 87:2264-2268, 1990), modified as in Karlin and Altschul, PNAS USA 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score = 100, wordlength =12. BLAST protein searches are performed with the XBLAST program, score =50, wordlength=3. To obtain gapped alignment for comparison purposes GappedBLAST is utilized as described in Altschul et al (Nucleic Acids Res. 25:3389-3402, 1997). When utilizing BLAST and GappedBLAST programs the default parameters of the respective programs (e.g., XBLAST and NBLAST) are used to obtain nucleotide sequences homologous to a nucleic acid molecule described herein.

The term "NAD(P)H oxidase activity", as described herein, refers to enzymatic activity of either the NAD(P)H oxidase or the NAD(P)H oxidase complex, as defined herein, whereby reactive oxygen species (ROS) are produced. Such enzymatic activity is readily established and procedures for this are well known to a skilled person. This activity is well known in the art and methods whereby this can be monitored are well known.

The term "inhibiting" with regards to ROS generating activity of the NAD(P)H oxidase or the NAD(P)H oxidase complex is meant the lowering of said activity to the range between 20%-100% of normal activity when measured with said methods. A preferred value of the inhibitory constant K_i is <10 μM, or more preferably <1 μM.

As defined herein, the term "NAD(P)H oxidase inhibitor" means any compound capable of lowering the activity of the NAD(P)H oxidase or the NAD(P)H oxidase complex, according to the above mentioned definition.

When activated, the NAD(P)H oxidase complex assembles at the plasma membrane and catalyses the single electron reduction of molecular O_2 to superoxide (O_2^-). In the presence of superoxide dismutase, O_2^- dismutates to hydrogen peroxide (H_2O_2) that can be converted to a hydroxyl radical (OH^-) in the presence of ferrous ions. The list of other free radicals originating from O_2^- that can be formed in the cell is longer, and will not be further discussed here. Several proteins are required for the formation of an active NAD(P)H oxidase complex and may include: p22phox, Mox2, Nox4, Nox5, DUOX1, DUOX2, (b5+b5R) oxidoreductase, p47phox, p67phox, p40phox, Rac-1, Rac-2 [Lambeth et al. (2000) Trends Biochem. Sci. 25: 459-461].

A fully active complex producing oxygen radicals in the presence of NAD(P)H, FAD, GTP and amphiphilic compounds can be reconstituted *in vitro* with individual recombinant proteins [Rotrosen et al., Journal of Biological Chemistry, 268:14256-60 (1993)].

The invention will now be demonstrated by the following examples. These examples are for the purpose of illustration only and are not intended to limit the scope of the invention in any way. The information necessary for carrying out these experiments is supplied in the references. Any variations and adjustments that need to be made for correct function of these assays (variations in pH, concentration ranges, etc) will be apparent for a skilled person.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Suitable methods and materials are described below, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

EXAMPLES

EXAMPLE 1: The NAD(P)H oxidase inhibitor DPI increases glucose uptake in rat skeletal muscle cells

Cell culture medium, fetal bovine serum, antibiotics, trypsin-EDTA were purchased from Life Technologies. Diphenylene iodonium (DPI), cytidine, bovine insulin, bovine serum albumin, and glucose oxidase were purchased from Sigma. 2-Deoxy-[^{3}H] glucose (specific activity 1102.6 GBq/mmol) was purchased from NEN Life Science Products and 2-Deoxy-[^{14}C] glucose from Amersham Pharmacia Biotech. Tissue culture plastics were purchased from Becton Dickinson.

Rat skeletal muscle L6-K cells were grown in minimal essential medium (α-MEM Glutamax I) containing 10% fetal bovine serum at 37°C, 5% CO_2. The cells were passaged twice weekly by treatment with trypsin-EDTA and transfer of 1/3 of the cells to new flasks with fresh culture medium. For differentiation into myotubes, 30,000 cells

were seeded in 1 ml in 24-well plates. When the cells were confluent, usually after 3 days, the medium was replaced by differentiation medium consisting of α-MEM, 2% fetal bovine serum and penicillin/streptomycin at a concentration of 100 U/ml and 100 µg/ml, respectively. The medium was replaced every 2-3 days. Between days 4-7, differentiation medium containing 1 mM cytidine was used. The cells were differentiated for 8-10 days before being used in experiments.

On the day before the glucose transport assay, the wells of the culture plate were emptied and 1 ml serum free DMEM containing 5 mM glucose and penicillin/ streptomycin was added. In some experiments the cells were treated over night with test compounds in 1 ml and additional treatments were added the next day to give a total volume of 2 ml. In these experiments, insulin (100-1000 nM) was added in 0.2 ml. When all treatments were performed after 20-24 h in serum free medium, a total volume of 1 ml was used. The wells were emptied and 0.5 ml prewarmed PBS without Ca^{2+}/Mg^{2+} containing 1 µCi/ml radioactive 2-deoxy-glucose added. After 10 min at 37°C, the wells were emptied and washed three times with cold PBS. The cell monolayer was solubilized in 0.5 ml 0.5 M NaOH for 3 h at room temperature. 400 µl was mixed with 8 ml scintillation fluid (Optiphase, Wallac) and counted in a scintillation counter (Packard TriCarb). Two 10-µl aliquots were used for determination of protein concentration using the method according to Bradford (Anal. Biochem., 1976, 72:248-54) from BioRad.

When differentiated L6 cells are incubated with the NAD(P)H oxidase inhibitor DPI [O´Donnell V.B. et al. (1993) Biochem. J. 290: 41-49] a significant increase in glucose uptake can be observed (Fig. 1). This increase is comparable to or greater than that caused by insulin. This effect is seen when cells are stimulated with 0.1-10 µM DPI for 1 h. A bell-shaped dose response curve for DPI with an optimum at 1 µM is recorded. The effect of suboptimal concentrations of DPI during a 1 h treatment could be stimulated further if insulin is added 30 min after DPI. However, insulin has little additional effect when the maximum effect of DPI is reached in the 1 h protocol (Fig. 1). The effective concentrations at which DPI stimulates glucose transport corresponds well to the concentrations inhibiting NAD(P)H oxidase activity in cell free systems [O'Donnell et al., Biochemical Journal, 290:41-9 (1993)]. These results suggest that DPI stimulates glucose transport via activation of the same mechanism as insulin. On the basis of the above results it is postulated that DPI enhances a constitutive activity of the insulin receptor and/or the intracellular insulin-signaling pathway. The existence of such

a constitutive activity is suggested from experiments in which adipocytes have been transfected with the tyrosine phosphatase PTP1B [Chen et al., Journal of Biological Chemistry, 272:8026-31 (1997)]. These data are compatible with DPI augmenting constitutive intracellular signaling via the same pathway that is used by insulin.

EXAMPLE 2: Glucose oxidase reduces the effect of DPI on glucose uptake

Assuming that the enhancing effect of DPI on insulin signaling was due to inhibition of ROS production, it was investigated whether an exogenous source of H_2O_2 could counteract the effect of DPI. To this end, L6 cells were treated with 25 mU/ml of glucose oxidase for 30 min before addition of DPI. Such a treatment has previously been shown to result in a steady production of micromolar concentrations of H_2O_2 that can freely pass the cell membrane and cause inhibition of insulin signaling [Tirosh, Potashnik et al., Journal of Biological Chemistry, 274:10595-602 (1999)].

It was found that glucose oxidase reduced the stimulatory effect of DPI by 68% and insulin stimulated glucose transport by 65% (Fig. 2). The available results suggest that H_2O_2 can counteract the effect of DPI in addition to inducing insulin resistance. This further strengthens the similarity between the effects of insulin and DPI and shows that DPI acts by inhibiting H_2O_2 production. In spite of superoxide being the primary product of NAD(P)H oxidase, H_2O_2 is the main effector in the cell since superoxide is converted to H_2O_2 by superoxide dismutase.

EXAMPLE 3: DPI decreases blood glucose levels in ob/ob mice

Studies were conducted *in vivo*, in an animal model of obesity characterized by insulin resistance. Eight-month old C57BL/6J ob/ob mice (M&B A/S, Denmark) were matched for sex, weight and fasting blood glucose concentrations. The animals were injected intraperitoneally once daily with DPI (1 mg/kg) or water for 4 days. On day 5, the animals were fasted for 2.5 h and then given an i.p. injection of human insulin 0.5 U/kg (Actrapid, Novo Nordisk, Denmark) and their blood glucose levels were monitored for 4 h by sampling from the tail. The glucose concentration was determined using a Glucometer Accutrend Sensor (Roche).

Without any overt side effects of the DPI treatment, the treated animals exhibited significantly lower blood glucose levels than the control group 1-4 h after injection of insulin, suggesting a decreased insulin resistance (Fig. 3).

EXAMPLE 4: Identification of agents inhibiting NAD(P)H oxidase

Methods to be used for identifying compounds that inhibit the activity of the NAD(P)H oxidase complex are illustrated.

(A) Neutrophil membrane and cytosol assay for superoxide mediated cytochrome c reduction (Diatchuk, V. et al. (1997) J. Biol. Chem. 272: 13292-13301). Sources of neutrophil membranes and cytosol from buffy coats of normal donors are obtainable from the Blood Bank. Enzyme cofactors and cytochrome c for detection of superoxide-mediated reduction are commercially available. The assay is based on a color change that occurs upon reduction of cytochrome c. This change can be measured as a change in light absorbance using a standard microplate spectrophotometer.

(B) Neutrophil membrane + recombinant $p47^{phox}$, $p67^{phox}$ and rac1 for superoxide-mediated cytochrome c reduction (absorbance) (Nisimoto, Y. et al. (1997) J. Biol. Chem. 272: 18834-18841).

(C) Fully recombinant NAD(P)H oxidase assay for superoxide mediated cytochrome c reduction [Rotrosen, D. et al, (1993) J. Biol. Chem. 268: 14256-14260].

(D) Fluorescence assay, which measures the interaction between rac and $p67^{phox}$ [Nisimoto, Y. et al. (1997) J. Biol. Chem. 272: 18834-18841]. This assay would limit the screening to detection of compounds interfering with this particular step in the activation of the oxidase. The fluorescent GTP analog 2'-(or-3')-*O*-(*N*-methylanthraniloyl) –βγ-imidoguanosine 5'-triphosphate (MANT-GMPPNP, available from Molecular Probes), binds tightly to Rac, and shows an increase in fluorescence when $p67^{phox}$ is added, indicating complex formation. Rac1 and Rac2 bind to $p67^{phox}$ with a 1:1 stoichiometry and with Kd values of 120 nM and 60 nM, respectively.

(E) Binding assay utilizing ^{125}I- or fluorescence labeled mastoparan. Mastoparan is a peptide present in wasp venom that has been shown to inhibit NAD(P)H oxidase activation, most likely via its ability to bind to $p67^{phox}$ [Tisch-Idelson, D., et al.(2001) Biochemical Pharmacology 61: 1063-1071].

(F) Test compounds can be analyzed in a nitroblue tetrazolium reduction assay utilizing a thioredoxin-$gp91^{phox}$ fusion protein. This protein has weak diaphorase activity in the presence of NAD(P)H and FAD and is inhibited by DPI.

(G) Test compounds can be added in appropriate amounts to cultured cells. The reactive oxygen species released from said cells may be measured with the use of a probe, resorufin, which becomes fluorescent in the presence of hydrogen peroxide and a peroxidase [Zhou, M. et al., (1997) Anal. Biochem., 253: 162-168].

Intracellular production of ROS can be measured with the use of various cell permeable analogs of dichlorofluorescin acetate as described by Xie, J.I. et al.[(1999) J. Biol. Chem. 274: 19323-19328].

5

CLAIMS

1. A method for identifying an agent that increases glucose uptake by a cell, the method comprising:

contacting a cell with a candidate agent that inhibits the activity of an NAD(P)H oxidase or an NAD(P)H oxidase complex;

measuring glucose uptake by the cell in the presence of the candidate agent; and

determining whether the candidate agent increases glucose uptake by the cell.

2. The method of claim 1, wherein the NAD(P)H oxidase or the NAD(P)H oxidase complex is a human NAD(P)H oxidase or a human NAD(P)H oxidase complex.

3. The method of claim 1, wherein the cell is a muscle cell.

4. The method of claim 1, wherein the cell is an adipocyte.

5. The method of claim 1, wherein the NAD(P)H oxidase or the NAD(P)H oxidase complex is selected from the group consisting of gp91phox, p22phox, Mox2, Nox4, Nox5, DUOX1, DUOX2, (b5+b5R) oxidoreductase, p47phox, p67phox, p40phox, Rac-1, and Rac-2.

6. The method of claim 1, wherein the candidate agent is selected from the group consisting of pyridine, imidazole, diethyl pyrocarbonate, chloromercuribenzoic acid, 4-(2-aminomethyl)-sulfonyl fluoride acetovanillone, and derivatives thereof.

7. The method of claim 1, further comprising comparing glucose uptake by the cell in the presence of the candidate agent with glucose uptake by a cell in the absence of the candidate agent.

8. The method of claim 1, further comprising contacting the candidate agent with the NAD(P)H oxidase or the NAD(P)H oxidase complex and determining that the candidate agent inhibits the activity of the NAD(P)H oxidase or the NAD(P)H oxidase complex.

9. A method for increasing glucose uptake in a cell, the method comprising contacting a cell with an amount of an inhibitor of an NAD(P)H oxidase or an NAD(P)H oxidase complex effective to increase glucose uptake by the cell.

10. The method of claim 9, further comprising detecting an increase in glucose uptake by the cell in response to the contacting of the cell with the inhibitor.

11. The method of claim 9, wherein the cell is a muscle cell.

12. The method of claim 9, wherein the cell is an adipocyte.

13. The method of claim 9, wherein the NAD(P)H oxidase or the NAD(P)H oxidase complex is selected from the group consisting of gp91phox, p22phox, Mox2, Nox4, Nox5, DUOX1, DUOX2, (b5+b5R) oxidoreductase, p47phox, p67phox, p40phox, Rac-1, and Rac-2.

14. The method of claim 9, wherein the NAD(P)H oxidase or the NAD(P)H oxidase complex is a human NAD(P)H oxidase or a human NAD(P)H oxidase complex.

15. The method of claim 9, wherein the inhibitor is selected from the group consisting of pyridine, imidazole, diethyl pyrocarbonate, chloromercuribenzoic acid, 4-(2-aminomethyl)-sulfonyl fluoride acetovanillone, and derivatives thereof.

16. A method for the treatment of a medical condition, the method comprising:

selecting an individual diagnosed as having a medical condition characterized by elevated levels of blood glucose; and

administering to the individual an amount of an inhibitor of an NAD(P)H oxidase or an NAD(P)H oxidase complex effective to reduce blood glucose levels in the individual.

17. The method of claim 16, further comprising detecting a reduction in blood glucose levels in the individual in response to the administration of the inhibitor.

18. The method of claim 16, wherein the medical condition is characterized by insulin resistance.

19. The method of claim 16, wherein the medical condition is characterized by a need for increased activity of the insulin receptor.

20. The method of claim 16, wherein the medical condition is characterized by a need for increased activity of the intracellular insulin-signaling pathway.

21. The method of claim 16, wherein the medical condition is diabetes.

22. The method of claim 21, wherein the medical condition is type II diabetes.

23. The method of claim 16, wherein the NAD(P)H oxidase or the NAD(P)H oxidase complex is selected from the group consisting of gp91phox, p22phox, Mox2, Nox4, Nox5, DUOX1, DUOX2, (b5+b5R) oxidoreductase, p47phox, p67phox, p40phox, Rac-1, and Rac-2.

24. The method of claim 16, wherein the NAD(P)H oxidase or the NAD(P)H oxidase complex is a human NAD(P)H oxidase or a human NAD(P)H oxidase complex.

25. The method of claim 16, wherein the inhibitor is selected from the group consisting of pyridine, imidazole, diethyl pyrocarbonate, chloromercuribenzoic acid, 4-(2-aminomethyl)-sulfonyl fluoride acetovanillone, and derivatives thereof.

26. Use of an inhibitor of an NAD(P)H oxidase or an NAD(P)H oxidase complex, effective to increase glucose uptake by the cell, in the manufacture of a medicament for increasing glucose uptake in a cell.

Fig. 1

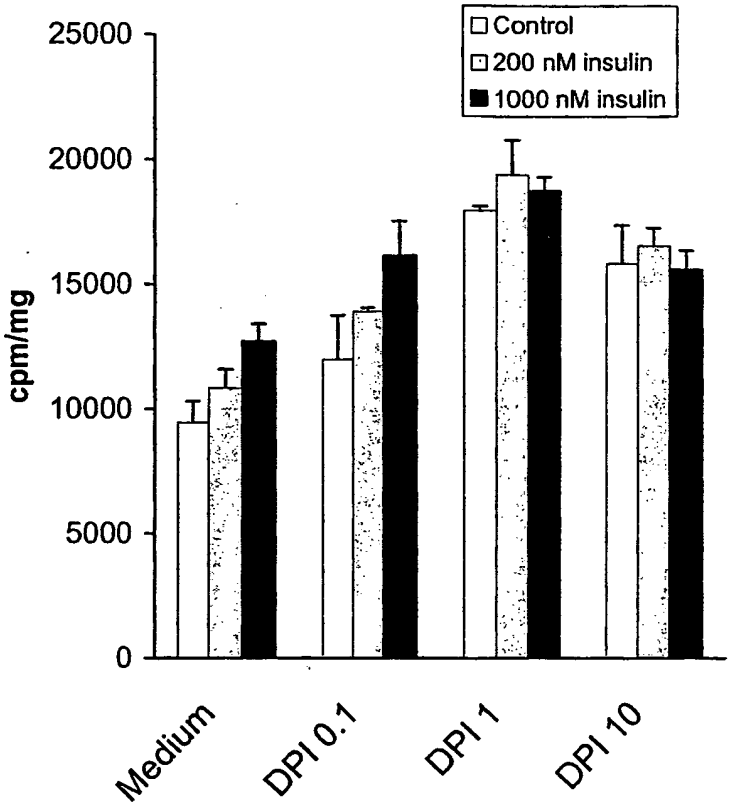
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Fig. 2

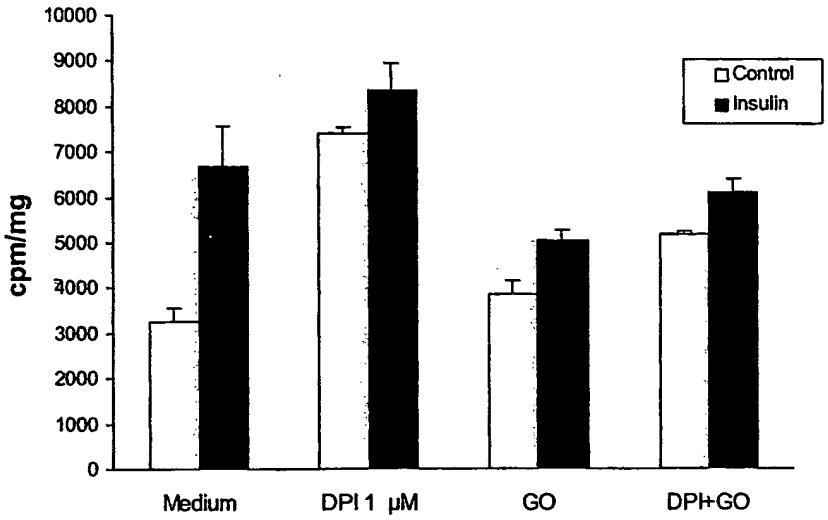
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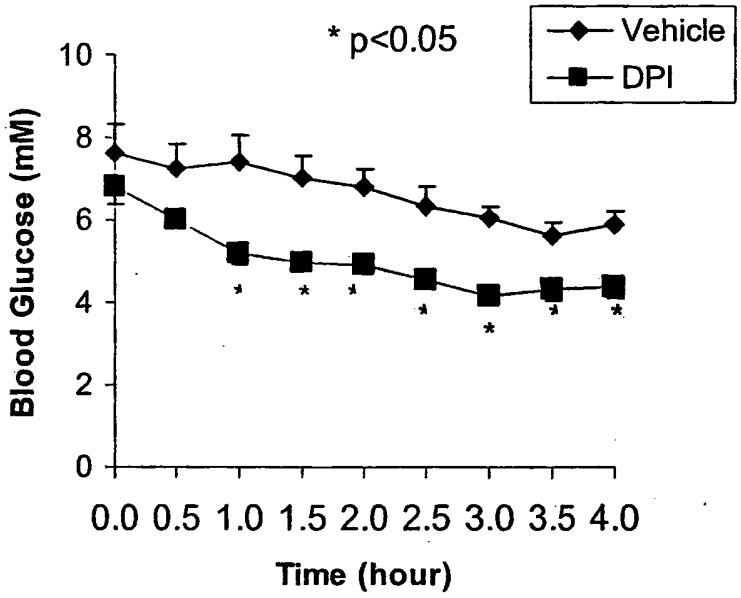
Fig. 3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Ala Glu Ala Arg Lys Lys Pro Ser Glu Glu Glu Ala Ala Ala Ala Ala
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Gly Gly Pro Pro Gly Gly Pro Gln Val Asn Pro Ile Pro Val Thr Asp
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Glu Val Val
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ctaccactgg agccagtccg aggaggccca gggacttctg gccgcacttt ccaagctggg 540

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Trp Tyr Glu Glu Glu Glu Ser Phe His Tyr Thr Arg Val Ile Leu Gly
35 40 45

Ser Thr Leu Ala Trp Ala Arg Ala Ser Ala Leu Cys Leu Asn Phe Asn
50 55 60

Cys Met Leu Ile Leu Ile Pro Val Ser Arg Asn Leu Ile Ser Phe Ile
65 70 75 80

Arg Gly Thr Ser Ile Cys Cys Arg Gly Pro Trp Arg Arg Gln Leu Asp
85 90 95

Lys Asn Leu Arg Phe His Lys Leu Val Ala Tyr Gly Ile Ala Val Asn
100 105 110

Ala Thr Ile His Ile Val Ala His Phe Phe Asn Leu Glu Arg Tyr His
115 120 125

Trp Ser Gln Ser Glu Glu Ala Gln Gly Leu Leu Ala Ala Leu Ser Lys
130 135 140

Leu Gly Asn Thr Pro Asn Glu Ser Tyr Leu Asn Pro Val Arg Thr Phe
145 150 155 160

Pro Thr Asn Thr Thr Thr Glu Leu Leu Arg Thr Ile Ala Gly Val Thr
165 170 175

Gly Leu Val Ile Ser Leu Ala Leu Val Leu Ile Met Thr Ser Ser Thr
180 185 190

Glu Phe Ile Arg Gln Ala Ser Tyr Glu Leu Phe Trp Tyr Thr His His
195 200 205

Val Phe Ile Val Phe Phe Leu Ser Leu Ala Ile His Gly Thr Gly Arg
210 215 220

Ile Val Arg Gly Gln Thr Gln Asp Ser Leu Ser Leu His Asn Ile Thr
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Phe Cys Arg Asp Arg Tyr Ala Glu Trp Gln Thr Val Ala Gln Cys Pro
245 250 255

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Val Pro Gln Phe Ser Gly Lys Glu Pro Ser Ala Trp Lys Trp Ile Leu
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Gly Pro Val Val Leu Tyr Ala Cys Glu Arg Ile Ile Arg Phe Trp Arg
        275                 280                 285

Phe Gln Gln Glu Val Val Ile Thr Lys Val Val Ser His Pro Ser Gly
    290                 295                 300

Val Leu Glu Leu His Met Lys Lys Arg Gly Phe Lys Met Ala Pro Gly
305                 310                 315                 320

Gln Tyr Ile Leu Val Gln Cys Pro Ala Ile Ser Ser Leu Glu Trp His
                325                 330                 335

Pro Phe Thr Leu Thr Ser Ala Pro Gln Glu Asp Phe Phe Ser Val His
            340                 345                 350

Ile Arg Ala Ala Gly Asp Trp Thr Ala Ala Leu Leu Glu Ala Phe Gly
        355                 360                 365

Ala Glu Gly Gln Ala Leu Gln Glu Pro Trp Ser Leu Pro Arg Leu Ala
    370                 375                 380

Val Asp Gly Pro Phe Gly Thr Ala Leu Thr Asp Val Phe His Tyr Pro
385                 390                 395                 400

Val Cys Val Cys Val Ala Ala Gly Ile Gly Val Thr Pro Phe Ala Ala
                405                 410                 415

Leu Leu Lys Ser Ile Trp Tyr Lys Cys Ser Glu Ala Gln Thr Pro Leu
            420                 425                 430

Lys Leu Ser Lys Val Tyr Phe Tyr Trp Ile Cys Arg Asp Ala Arg Ala
        435                 440                 445

Phe Glu Trp Phe Ala Asp Leu Leu Leu Ser Leu Glu Thr Arg Met Ser
    450                 455                 460

Glu Gln Gly Lys Thr His Phe Leu Ser Tyr His Ile Phe Leu Thr Gly
465                 470                 475                 480

Trp Asp Glu Asn Gln Ala Leu His Ile Ala Leu His Trp Asp Glu Asn
                485                 490                 495

Thr Asp Val Ile Thr Gly Leu Lys Gln Lys Thr Phe Tyr Gly Arg Pro
            500                 505                 510

Asn Trp Asn Asn Glu Phe Lys Gln Ile Ala Tyr Asn His Pro Ser Ser
        515                 520                 525

Ser Ile Gly Val Phe Phe Cys Gly Pro Lys Ala Leu Ser Arg Thr Leu
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Gln Lys Met Cys His Leu Tyr Ser Ser Ala Asp Pro Arg Gly Val His
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Phe Tyr Tyr Asn Lys Glu Ser Phe
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            20                  25                  30

Thr Phe Leu Leu Tyr Asn Gln Gly Pro Glu Tyr His Tyr Leu His Gln
        35                  40                  45

Met Leu Gly Leu Gly Leu Cys Leu Ser Arg Ala Ser Ala Ser Val Leu
    50                  55                  60

Asn Leu Asn Cys Ser Leu Ile Leu Leu Pro Met Cys Arg Thr Leu Leu
65                  70                  75                  80

Ala Tyr Leu Arg Gly Ser Gln Lys Val Pro Ser Arg Arg Thr Arg Arg
                85                  90                  95

Leu Leu Asp Lys Ser Arg Thr Phe His Ile Thr Cys Gly Val Thr Ile
            100                 105                 110

Cys Ile Phe Ser Gly Val His Val Ala Ala His Leu Val Asn Ala Leu
        115                 120                 125

Asn Phe Ser Val Asn Tyr Ser Glu Asp Phe Val Glu Leu Asn Ala Ala
    130                 135                 140

Arg Tyr Arg Asp Glu Asp Pro Arg Lys Leu Leu Phe Thr Thr Val Pro
145                 150                 155                 160

Gly Leu Thr Gly Val Cys Met Val Val Val Leu Phe Leu Met Ile Thr
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Ala Ser Thr Tyr Ala Ile Arg Val Ser Asn Tyr Asp Ile Phe Trp Tyr
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Thr His Asn Leu Phe Phe Val Phe Tyr Met Leu Leu Thr Leu His Val
        195                 200                 205

Ser Gly Gly Leu Leu Lys Tyr Gln Thr Asn Leu Asp Thr His Pro Pro
    210                 215                 220

Gly Cys Ile Ser Leu Asn Arg Thr Ser Ser Gln Asn Ile Ser Leu Pro
225                 230                 235                 240

Glu Tyr Phe Ser Glu His Phe His Glu Pro Phe Pro Glu Gly Phe Ser
                245                 250                 255

Lys Pro Ala Glu Phe Thr Gln His Lys Phe Val Lys Ile Cys Met Glu
            260                 265                 270

Glu Pro Arg Phe Gln Ala Asn Phe Pro Gln Thr Trp Leu Trp Ile Ser
        275                 280                 285

Gly Pro Leu Cys Leu Tyr Cys Ala Glu Arg Leu Tyr Arg Tyr Ile Arg
    290                 295                 300

Ser Asn Lys Pro Val Thr Ile Ile Ser Val Ile Ser His Pro Ser Asp
305                 310                 315                 320

Val Met Glu Ile Arg Met Val Lys Glu Asn Phe Lys Ala Arg Pro Gly
                325                 330                 335

Gln Tyr Ile Thr Leu His Cys Pro Ser Val Ser Ala Leu Glu Asn His
            340                 345                 350

Pro Phe Thr Leu Thr Met Cys Pro Thr Glu Thr Lys Ala Thr Phe Gly
        355                 360                 365

Val His Leu Lys Ile Val Gly Asp Trp Thr Glu Arg Phe Arg Asp Leu
    370                 375                 380

Leu Leu Pro Pro Ser Ser Gln Asp Ser Glu Ile Leu Pro Phe Ile Gln
385                 390                 395                 400

Ser Arg Asn Tyr Pro Lys Leu Tyr Ile Asp Gly Pro Phe Gly Ser Pro
                405                 410                 415

Phe Glu Glu Ser Leu Asn Tyr Glu Val Ser Leu Cys Val Ala Gly Gly
            420                 425                 430

Ile Gly Val Thr Pro Phe Ala Ser Ile Leu Asn Thr Leu Leu Asp Asp
        435                 440                 445

Trp Lys Pro Tyr Lys Leu Arg Arg Leu Tyr Phe Ile Trp Val Cys Arg
    450                 455                 460

Asp Ile Gln Ser Phe Arg Trp Phe Ala Asp Leu Leu Cys Met Leu His
465                 470                 475                 480

Asn Lys Phe Trp Gln Glu Asn Arg Pro Asp Tyr Val Asn Ile Gln Leu
                485                 490                 495
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Tyr Leu Ser Gln Thr Asp Gly Ile Gln Lys Ile Ile Gly Glu Lys Tyr
500 505 510

His Ala Leu Asn Ser Arg Leu Phe Ile Gly Arg Pro Arg Trp Lys Leu
515 520 525

Leu Phe Asp Glu Ile Ala Lys Tyr Asn Arg Gly Lys Thr Val Gly Val
530 535 540

Phe Cys Cys Gly Pro Asn Ser Leu Ser Lys Thr Leu His Lys Leu Ser
545 550 555 560

Asn Gln Asn Asn Ser Tyr Gly Thr Arg Phe Glu Tyr Asn Lys Glu Ser
565 570 575

Phe Ser

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<211> 2223
<212> DNA
<213> Homo sapiens

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<210> 10
<211> 565
<212> PRT
<213> Homo sapiens

<400> 10

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Pro Arg Pro Arg Pro Arg Arg Pro Arg Gln Leu Thr Arg Ala Tyr Trp
20 25 30

His Asn His Arg Ser Gln Leu Phe Cys Leu Ala Thr Tyr Ala Gly Leu
35 40 45

His Val Leu Leu Phe Gly Leu Ala Ala Ser Ala His Arg Asp Leu Gly
50 55 60

Ala Ser Val Met Val Ala Lys Gly Cys Gly Gln Cys Leu Asn Phe Asp
65 70 75 80

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Cys Ser Phe Ile Ala Val Leu Met Leu Arg Arg Cys Leu Thr Trp Leu
                85                  90                  95

Arg Ala Thr Trp Leu Ala Gln Val Leu Pro Leu Asp Gln Asn Ile Gln
            100                 105                 110

Phe His Gln Leu Met Gly Tyr Val Val Val Gly Leu Ser Leu Val His
        115                 120                 125

Thr Val Ala His Thr Val Asn Phe Val Leu Gln Ala Gln Ala Glu Ala
    130                 135                 140

Ser Pro Phe Gln Phe Trp Glu Leu Leu Leu Thr Thr Arg Pro Gly Ile
145                 150                 155                 160

Gly Trp Val His Gly Ser Ala Ser Pro Thr Gly Val Ala Leu Leu Leu
                165                 170                 175

Leu Leu Leu Leu Met Phe Ile Cys Ser Ser Ser Cys Ile Arg Arg Ser
            180                 185                 190

Gly His Phe Glu Val Phe Tyr Trp Thr His Leu Ser Tyr Leu Leu Val
        195                 200                 205

Trp Leu Leu Leu Ile Phe His Gly Pro Asn Phe Trp Lys Trp Leu Leu
    210                 215                 220

Val Pro Gly Ile Leu Phe Phe Leu Glu Lys Ala Ile Gly Leu Ala Val
225                 230                 235                 240

Ser Arg Met Ala Ala Val Cys Ile Met Glu Val Asn Leu Leu Pro Ser
                245                 250                 255

Lys Val Thr His Leu Leu Ile Lys Arg Pro Pro Phe Phe His Tyr Arg
            260                 265                 270

Pro Gly Asp Tyr Leu Tyr Leu Asn Ile Pro Thr Ile Ala Arg Tyr Glu
        275                 280                 285

Trp His Pro Phe Thr Ile Ser Ser Ala Pro Glu Gln Lys Asp Thr Ile
    290                 295                 300

Trp Leu His Ile Arg Ser Gln Gly Gln Trp Thr Asn Arg Leu Tyr Glu
305                 310                 315                 320

Ser Phe Lys Ala Ser Asp Pro Leu Gly Arg Gly Ser Lys Arg Leu Ser
                325                 330                 335

Arg Ser Val Thr Met Arg Lys Ser Gln Arg Ser Ser Lys Gly Ser Glu
            340                 345                 350

Ile Leu Leu Glu Lys His Lys Phe Cys Asn Ile Lys Cys Tyr Ile Asp
        355                 360                 365

Gly Pro Tyr Gly Thr Pro Thr Arg Arg Ile Phe Ala Ser Glu His Ala
    370                 375                 380

Val Leu Ile Gly Ala Gly Ile Gly Ile Thr Pro Phe Ala Ser Ile Leu
385                 390                 395                 400
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Gln Ser Ile Met Tyr Arg His Gln Lys Arg Lys His Thr Cys Pro Ser
405 410 415

Cys Gln His Ser Trp Ile Glu Gly Val Gln Asp Asn Met Lys Leu His
420 425 430

Lys Val Asp Phe Ile Trp Ile Asn Arg Asp Gln Arg Ser Phe Glu Trp
435 440 445

Phe Val Ser Leu Leu Thr Lys Leu Glu Met Asp Gln Ala Glu Glu Ala
450 455 460

Gln Tyr Gly Arg Phe Leu Glu Leu His Met Tyr Met Thr Ser Ala Leu
465 470 475 480

Gly Lys Asn Asp Met Lys Ala Ile Gly Leu Gln Met Ala Leu Asp Leu
485 490 495

Leu Ala Asn Lys Glu Lys Lys Asp Ser Ile Thr Gly Leu Gln Thr Arg
500 505 510

Thr Gln Pro Gly Arg Pro Asp Trp Ser Lys Val Phe Gln Lys Val Ala
515 520 525

Ala Glu Lys Lys Gly Lys Val Gln Val Phe Phe Cys Gly Ser Pro Ala
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Leu Ala Lys Val Leu Lys Gly His Cys Glu Lys Phe Gly Phe Arg Phe
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Phe Gln Glu Asn Phe
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<210> 11

<211> 5494

<212> DNA

<213> Homo sapiens

<400> 11

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Thr Ile Ser Arg Gly Pro Ala Gly Leu Ala Ser Leu Arg Asn Arg Thr
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Val Leu Gly Val Phe Phe Gly Tyr His Val Leu Ser Asp Leu Val Ser
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Val Glu Thr Pro Gly Cys Pro Ala Glu Phe Leu Asn Ile Arg Ile Pro
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Pro Gly Asp Pro Met Phe Asp Pro Asp Gln Arg Gly Asp Val Val Leu
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Ala Ile Tyr Gly Ser Ser His Ser Trp Ser Asp Ala Leu Arg Ser Phe
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tattgtagag atgtaccaca gtttgtttat tcttctgttg atggacgttt gggttgtttc 6300

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<213> Homo sapiens

<400> 14

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Thr Gly Ser Leu Gly Pro Ser Gly Ser Gln Asp Ala Leu Ser Leu Pro
            20                  25                  30

Trp Glu Val Gln Arg Tyr Asp Gly Trp Phe Asn Asn Leu Arg His His
        35                  40                  45

Glu Arg Gly Ala Val Gly Cys Arg Leu Gln Arg Arg Val Pro Ala Asn
    50                  55                  60

Tyr Ala Asp Gly Val Tyr Gln Ala Leu Glu Glu Pro Gln Leu Pro Asn
65                  70                  75                  80

Pro Arg Arg Leu Ser Asn Ala Ala Thr Arg Gly Ile Ala Gly Leu Pro
                85                  90                  95

Ser Leu His Asn Arg Thr Val Leu Gly Val Phe Phe Gly Tyr His Val
            100                 105                 110

Leu Ser Asp Val Val Ser Val Glu Thr Pro Gly Cys Pro Ala Glu Phe
        115                 120                 125
```

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Leu Asn Ile Arg Ile Pro Pro Gly Asp Leu Val Phe Asp Pro Asp Gln
    130                 135                 140

Arg Gly Asp Val Val Leu Pro Phe Gln Arg Ser Arg Trp Asp Pro Glu
145                 150                 155                 160

Thr Gly Arg Ser Pro Ser Asn Pro Arg Asp Leu Ala Asn Gln Val Thr
                165                 170                 175

Gly Trp Leu Asp Gly Ser Ala Ile Tyr Gly Ser Ser His Ser Trp Ser
            180                 185                 190

Asp Ala Leu Arg Ser Phe Ser Gly Gly Gln Leu Ala Ser Gly Pro Asp
        195                 200                 205

Pro Ala Phe Pro Arg Asp Ser Gln Asn Pro Leu Leu Met Trp Ala Ala
    210                 215                 220

Pro Asp Pro Ala Thr Gly Gln Asn Gly Pro Arg Gly Leu Tyr Ala Phe
225                 230                 235                 240

Gly Ala Glu Arg Gly Asn Arg Glu Pro Phe Leu Gln Ala Leu Gly Leu
                245                 250                 255

Leu Trp Phe Arg Tyr His Asn Leu Trp Ala Gln Arg Leu Ala Arg Gln
            260                 265                 270

His Pro Asp Trp Glu Asp Glu Glu Leu Phe Gln His Ala Arg Lys Arg
        275                 280                 285

Val Ile Ala Thr Tyr Gln Asn Ile Ala Val Tyr Glu Trp Leu Pro Ser
    290                 295                 300

Phe Leu Gln Lys Thr Leu Pro Glu Tyr Thr Gly Tyr Arg Pro Phe Leu
305                 310                 315                 320

Asp Pro Ser Ile Ser Pro Glu Phe Val Val Ala Ser Glu Gln Phe Phe
                325                 330                 335

Ser Thr Met Val Pro Pro Gly Val Tyr Met Arg Asn Ala Ser Cys His
            340                 345                 350

Phe Arg Lys Val Leu Asn Lys Gly Phe Gln Ser Ser Gln Ala Leu Arg
        355                 360                 365

Val Cys Asn Asn Tyr Trp Ile Arg Glu Asn Pro Asn Leu Asn Ser Thr
    370                 375                 380

Gln Glu Val Asn Glu Leu Leu Leu Gly Met Ala Ser Gln Ile Ser Glu
385                 390                 395                 400

Leu Glu Asp Asn Ile Val Val Glu Asp Leu Arg Asp Tyr Trp Pro Gly
                405                 410                 415

Pro Gly Lys Phe Ser Arg Thr Asp Tyr Val Ala Ser Ser Ile Gln Arg
            420                 425                 430

Gly Arg Asp Met Gly Leu Pro Ser Tyr Ser Gln Ala Leu Leu Ala Phe
        435                 440                 445
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Gly Leu Asp Ile Pro Arg Asn Trp Ser Asp Leu Asn Pro Asn Val Asp
    450                 455                 460

Pro Gln Val Leu Glu Ala Thr Ala Ala Leu Tyr Asn Gln Asp Leu Ser
465                 470                 475                 480

Gln Leu Glu Leu Leu Leu Gly Gly Leu Leu Glu Ser His Gly Asp Pro
                485                 490                 495

Gly Pro Leu Phe Ser Ala Ile Val Leu Asp Gln Phe Val Arg Leu Arg
            500                 505                 510

Asp Gly Asp Arg Tyr Trp Phe Glu Asn Thr Arg Asn Gly Leu Phe Ser
        515                 520                 525

Lys Lys Glu Ile Glu Asp Ile Arg Asn Thr Thr Leu Arg Asp Val Leu
    530                 535                 540

Val Ala Val Ile Asn Ile Asp Pro Ser Ala Leu Gln Pro Asn Val Phe
545                 550                 555                 560

Val Trp His Lys Gly Ala Pro Cys Pro Gln Pro Lys Gln Leu Thr Thr
                565                 570                 575

Asp Gly Leu Pro Gln Cys Ala Pro Leu Thr Val Leu Asp Phe Phe Glu
            580                 585                 590

Gly Ser Ser Pro Gly Phe Ala Ile Thr Ile Ile Ala Leu Cys Cys Leu
        595                 600                 605

Pro Leu Val Ser Leu Leu Leu Ser Gly Val Val Ala Tyr Phe Arg Gly
    610                 615                 620

Arg Glu His Lys Lys Leu Gln Lys Lys Leu Lys Glu Ser Val Lys Lys
625                 630                 635                 640

Glu Ala Ala Lys Asp Gly Val Pro Ala Met Glu Trp Pro Gly Pro Lys
                645                 650                 655

Glu Arg Ser Ser Pro Ile Ile Ile Gln Leu Leu Ser Asp Arg Cys Leu
            660                 665                 670

Gln Val Leu Asn Arg His Leu Thr Val Leu Arg Val Val Gln Leu Gln
        675                 680                 685

Pro Leu Gln Gln Val Asn Leu Ile Leu Ser Asn Asn Arg Gly Cys Arg
    690                 695                 700

Thr Leu Leu Leu Lys Ile Pro Lys Glu Tyr Asp Leu Val Leu Leu Phe
705                 710                 715                 720

Ser Ser Glu Glu Glu Arg Gly Ala Phe Val Gln Gln Leu Trp Asp Phe
                725                 730                 735

Cys Val Arg Trp Ala Leu Gly Leu His Val Ala Glu Met Ser Glu Lys
            740                 745                 750

Glu Leu Phe Arg Lys Ala Val Thr Lys Gln Gln Arg Glu Arg Ile Leu
        755                 760                 765
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Glu Ile Phe Phe Arg His Leu Phe Ala Gln Val Leu Asp Ile Asn Gln
    770                 775                 780

Ala Asp Ala Gly Thr Leu Pro Leu Asp Ser Ser Gln Lys Val Arg Glu
785                 790                 795                 800

Ala Leu Thr Cys Glu Leu Ser Arg Ala Glu Phe Ala Glu Ser Leu Gly
                805                 810                 815

Leu Lys Pro Gln Asp Met Phe Val Glu Ser Met Phe Ser Leu Ala Asp
            820                 825                 830

Lys Asp Gly Asn Gly Tyr Leu Ser Phe Arg Glu Phe Leu Asp Ile Leu
        835                 840                 845

Val Val Phe Met Lys Gly Ser Pro Glu Asp Lys Ser Arg Leu Met Phe
    850                 855                 860

Thr Met Tyr Asp Leu Asp Glu Asn Gly Phe Leu Ser Lys Asp Glu Phe
865                 870                 875                 880

Phe Thr Met Met Arg Ser Phe Ile Glu Ile Ser Asn Asn Cys Leu Ser
                885                 890                 895

Lys Ala Gln Leu Ala Glu Val Val Glu Ser Met Phe Arg Glu Ser Gly
            900                 905                 910

Phe Gln Asp Lys Glu Glu Leu Thr Trp Glu Asp Phe His Phe Met Leu
        915                 920                 925

Arg Asp His Asp Ser Glu Leu Arg Phe Thr Gln Leu Cys Val Lys Gly
    930                 935                 940

Gly Gly Gly Gly Gly Asn Gly Ile Arg Asp Ile Phe Lys Gln Asn Ile
945                 950                 955                 960

Ser Cys Arg Val Ser Phe Ile Thr Arg Thr Pro Gly Glu Arg Ser His
                965                 970                 975

Pro Gln Gly Leu Gly Pro Pro Val Pro Glu Ala Pro Glu Leu Gly Gly
            980                 985                 990

Pro Gly Leu Lys Lys Arg Phe Gly Lys Lys Ala Ala Val Pro Thr Pro
        995                 1000                1005

Arg Leu Tyr Thr Glu Ala Leu Gln Glu Lys Met Gln Arg Gly Phe
    1010                1015                1020

Leu Ala Gln Lys Leu Gln Gln Tyr Lys Arg Phe Val Glu Asn Tyr
    1025                1030                1035

Arg Arg His Ile Val Cys Val Ala Ile Phe Ser Ala Ile Cys Val
    1040                1045                1050

Gly Val Phe Ala Asp Arg Ala Tyr Tyr Tyr Gly Phe Ala Leu Pro
    1055                1060                1065

Pro Ser Asp Ile Ala Gln Thr Thr Leu Val Gly Ile Ile Leu Ser
    1070                1075                1080
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Arg Gly Thr Ala Ala Ser Val Ser Phe Met Phe Ser Tyr Ile Leu
1085 1090 1095

Leu Thr Met Cys Arg Asn Leu Ile Thr Phe Leu Arg Glu Thr Phe
1100 1105 1110

Leu Asn Arg Tyr Val Pro Phe Asp Ala Ala Val Asp Phe His Arg
1115 1120 1125

Trp Ile Ala Met Ala Ala Val Val Leu Ala Ile Leu His Ser Ala
1130 1135 1140

Gly His Ala Val Asn Val Tyr Ile Phe Ser Val Ser Pro Leu Ser
1145 1150 1155

Leu Leu Ala Cys Ile Phe Pro Asn Val Phe Val Asn Asp Gly Ser
1160 1165 1170

Lys Leu Pro Gln Lys Phe Tyr Trp Trp Phe Phe Gln Thr Val Pro
1175 1180 1185

Gly Met Thr Gly Val Leu Leu Leu Leu Val Leu Ala Ile Met Tyr
1190 1195 1200

Val Phe Ala Ser His His Phe Arg Arg Arg Ser Phe Arg Gly Phe
1205 1210 1215

Trp Leu Thr His His Leu Tyr Ile Leu Leu Tyr Ala Leu Leu Ile
1220 1225 1230

Ile His Gly Ser Tyr Ala Leu Ile Gln Leu Pro Thr Phe His Ile
1235 1240 1245

Tyr Phe Leu Val Pro Ala Ile Ile Tyr Gly Gly Asp Lys Leu Val
1250 1255 1260

Ser Leu Ser Arg Lys Lys Val Glu Ile Ser Val Val Lys Ala Glu
1265 1270 1275

Leu Leu Pro Ser Gly Val Thr Tyr Leu Gln Phe Gln Arg Pro Gln
1280 1285 1290

Gly Phe Glu Tyr Lys Ser Gly Gln Trp Val Arg Ile Ala Cys Leu
1295 1300 1305

Ala Leu Gly Thr Thr Glu Tyr His Pro Phe Thr Leu Thr Ser Ala
1310 1315 1320

Pro His Glu Asp Thr Leu Ser Leu His Ile Arg Ala Val Gly Pro
1325 1330 1335

Trp Thr Thr Arg Leu Arg Glu Ile Tyr Ser Ser Pro Lys Gly Asn
1340 1345 1350

Gly Cys Ala Gly Tyr Pro Lys Leu Tyr Leu Asp Gly Pro Phe Gly
1355 1360 1365

Glu Gly His Gln Glu Trp His Lys Phe Glu Val Ser Val Leu Val
1370 1375 1380

Gly Gly Gly Ile Gly Val Thr Pro Phe Ala Ser Ile Leu Lys Asp
1385 1390 1395

Leu Val Phe Lys Ser Ser Leu Gly Ser Gln Met Leu Cys Lys Lys
1400 1405 1410

Ile Tyr Phe Ile Trp Val Thr Arg Thr Gln Arg Gln Phe Glu Trp
1415 1420 1425

Leu Ala Asp Ile Ile Gln Glu Val Glu Glu Asn Asp His Gln Asp
1430 1435 1440

Leu Val Ser Val His Ile Tyr Val Thr Gln Leu Ala Glu Lys Phe
1445 1450 1455

Asp Leu Arg Thr Thr Met Leu Tyr Ile Cys Glu Arg His Phe Gln
1460 1465 1470

Lys Val Leu Asn Arg Ser Leu Phe Thr Gly Leu Arg Ser Ile Thr
1475 1480 1485

His Phe Gly Arg Pro Pro Phe Glu Pro Phe Phe Asn Ser Leu Gln
1490 1495 1500

Glu Val His Pro Gln Val Arg Lys Ile Gly Val Phe Ser Cys Gly
1505 1510 1515

Pro Pro Gly Met Thr Lys Asn Val Glu Lys Ala Cys Gln Leu Val
1520 1525 1530

Asn Arg Gln Asp Arg Ala His Phe Met His His Tyr Glu Asn Phe
1535 1540 1545

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gaagatgaac taatgagagc agcaggatca gatggtactg aacttttga tcaggttcat 240

cgttgggtca attatgaatc catgctgaaa gaatgcctgg ttggcagaat ggccattaaa 300

cctgctgttc tgaaagacta tcgtgaggag gaaaagaaag tcttaaatgg catgcttccc 360

aagagccaag tgacagatac acttgccaaa gaaggtccta gttatccaag ctatgattgg 420

ttccaaacag actctttagt caccattgcc atatatacta aacagaagga tatcaattta 480

gactcaatta tagttgatca tcagaatgat tcctttagag cagaaacaat tattaaggat 540

tgtttatatc ttatacatat tgggctaagc catgaggttc aggaagattt ttctgtgcgg 600

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aaggttaact agaatccagc cttcagtttc ttaaatgaaa tcaaatgttc cttcagtaca 1620

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<213> Homo sapiens

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Lys Gly Arg Leu Ile Glu Val Thr Glu Glu Glu Leu Lys Lys His Asn
20 25 30

Lys Lys Asp Asp Cys Trp Ile Cys Ile Arg Gly Phe Val Tyr Asn Val
35 40 45

Ser Pro Tyr Met Glu Tyr His Pro Gly Gly Glu Asp Glu Leu Met Arg
50 55 60

Ala Ala Gly Ser Asp Gly Thr Glu Leu Phe Asp Gln Val His Arg Trp
65 70 75 80

Val Asn Tyr Glu Ser Met Leu Lys Glu Cys Leu Val Gly Arg Met Ala
85 90 95

Ile Lys Pro Ala Val Leu Lys Asp Tyr Arg Glu Glu Glu Lys Lys Val
100 105 110

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Leu Asn Gly Met Leu Pro Lys Ser Gln Val Thr Asp Thr Leu Ala Lys
        115                 120                 125

Glu Gly Pro Ser Tyr Pro Ser Tyr Asp Trp Phe Gln Thr Asp Ser Leu
    130                 135                 140

Val Thr Ile Ala Ile Tyr Thr Lys Gln Lys Asp Ile Asn Leu Asp Ser
145                 150                 155                 160

Ile Ile Val Asp His Gln Asn Asp Ser Phe Arg Ala Glu Thr Ile Ile
                165                 170                 175

Lys Asp Cys Leu Tyr Leu Ile His Ile Gly Leu Ser His Glu Val Gln
            180                 185                 190

Glu Asp Phe Ser Val Arg Val Val Glu Ser Val Gly Lys Ile Glu Ile
        195                 200                 205

Val Leu Gln Lys Lys Glu Asn Thr Ser Trp Asp Phe Leu Gly His Pro
    210                 215                 220

Leu Lys Asn His Asn Ser Leu Ile Pro Arg Lys Asp Thr Gly Leu Tyr
225                 230                 235                 240

Tyr Arg Lys Cys Gln Leu Ile Ser Lys Glu Asp Val Thr His Asp Thr
                245                 250                 255

Arg Leu Phe Cys Leu Met Leu Pro Pro Ser Thr His Leu Gln Val Pro
            260                 265                 270

Ile Gly Gln His Val Tyr Leu Lys Leu Pro Ile Thr Gly Thr Glu Ile
        275                 280                 285

Val Lys Pro Tyr Thr Pro Val Ser Gly Ser Leu Leu Ser Glu Phe Lys
    290                 295                 300

Glu Pro Val Leu Pro Asn Asn Lys Tyr Ile Tyr Phe Leu Ile Lys Ile
305                 310                 315                 320

Tyr Pro Thr Gly Leu Phe Thr Pro Glu Leu Asp Arg Leu Gln Ile Gly
                325                 330                 335

Asp Phe Val Ser Val Ser Ser Pro Glu Gly Asn Phe Lys Ile Ser Lys
            340                 345                 350

Phe Gln Glu Leu Glu Asp Leu Phe Leu Leu Ala Ala Gly Thr Gly Phe
        355                 360                 365

Thr Pro Met Val Lys Ile Leu Asn Tyr Ala Leu Thr Asp Ile Pro Ser
    370                 375                 380

Leu Arg Lys Val Lys Leu Met Phe Phe Asn Lys Thr Glu Asp Asp Ile
385                 390                 395                 400

Ile Trp Arg Ser Gln Leu Glu Lys Leu Ala Phe Lys Asp Lys Arg Leu
                405                 410                 415

Asp Val Glu Phe Val Leu Ser Ala Pro Ile Ser Glu Trp Asn Gly Lys
            420                 425                 430
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Gln Gly His Ile Ser Pro Ala Leu Leu Ser Glu Phe Leu Lys Arg Asn
435 440 445

Leu Asp Lys Ser Lys Val Leu Val Cys Ile Cys Gly Pro Val Pro Phe
450 455 460

Thr Glu Gln Gly Val Arg Leu Leu His Asp Leu Asn Phe Ser Lys Asn
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Glu Ile His Ser Phe Thr Ala
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<211> 1340
<212> DNA
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gaaggtggtc taccggcgct tcaccgagat ctacgagttc cataaaacct taaaagaaat 180

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ctgcagcacg ctcatgagcc tgcccaccaa gatctcccgc tgtccccacc tcctcgactt 360

cttcaaggtg cgccctgatg acctcaagct ccccacggac aaccagacaa aaaagccaga 420

gacatacttg atgcccaaag atggcaagag taccgcgaca gacatcaccg gccccatcat 480

cctgcagacg taccgcgcca ttgccgacta cgagaagacc tcgggctccg agatggctct 540

gtccacgggg gacgtggtgg aggtcgtgga gaagagcgag agcggttggt ggttctgtca 600

gatgaaagca aagcgaggct ggatcccagc atccttcctc gagcccctgg acagtcctga 660

cgagacggaa gaccctgagc ccaactatgc aggtgagcca tacgtcgcca tcaaggccta 720

cactgctgtg gaggggacg aggtgtccct gctcgagggt gaagctgttg aggtcattca 780

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<210> 18
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<213> Homo sapiens

<400> 18

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Arg Phe Val Pro Ser Gln His Tyr Val Tyr Met Phe Leu Val Lys Trp
            20                  25                  30

Gln Asp Leu Ser Glu Lys Val Val Tyr Arg Arg Phe Thr Glu Ile Tyr
        35                  40                  45

Glu Phe His Lys Thr Leu Lys Glu Met Phe Pro Ile Glu Ala Gly Ala
    50                  55                  60

Ile Asn Pro Glu Asn Arg Ile Ile Pro His Leu Pro Ala Pro Lys Trp
65                  70                  75                  80

Phe Asp Gly Gln Arg Ala Ala Glu Asn Arg Gln Gly Thr Leu Thr Glu
                85                  90                  95

Tyr Cys Ser Thr Leu Met Ser Leu Pro Thr Lys Ile Ser Arg Cys Pro
            100                 105                 110

His Leu Leu Asp Phe Phe Lys Val Arg Pro Asp Asp Leu Lys Leu Pro
        115                 120                 125

Thr Asp Asn Gln Thr Lys Lys Pro Glu Thr Tyr Leu Met Pro Lys Asp
    130                 135                 140

Gly Lys Ser Thr Ala Thr Asp Ile Thr Gly Pro Ile Ile Leu Gln Thr
145                 150                 155                 160

Tyr Arg Ala Ile Ala Asp Tyr Glu Lys Thr Ser Gly Ser Glu Met Ala
                165                 170                 175

Leu Ser Thr Gly Asp Val Val Glu Val Val Glu Lys Ser Glu Ser Gly
            180                 185                 190

Trp Trp Phe Cys Gln Met Lys Ala Lys Arg Gly Trp Ile Pro Ala Ser
        195                 200                 205

Phe Leu Glu Pro Leu Asp Ser Pro Asp Glu Thr Glu Asp Pro Glu Pro
    210                 215                 220

Asn Tyr Ala Gly Glu Pro Tyr Val Ala Ile Lys Ala Tyr Thr Ala Val
225                 230                 235                 240

Glu Gly Asp Glu Val Ser Leu Leu Glu Gly Glu Ala Val Glu Val Ile
                245                 250                 255

His Lys Leu Leu Asp Gly Trp Trp Val Ile Arg Lys Asp Asp Val Thr
            260                 265                 270
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Gly Tyr Phe Pro Ser Met Tyr Leu Gln Lys Ser Gly Gln Asp Val Ser
275 280 285

Gln Ala Gln Arg Gln Ile Lys Arg Gly Ala Pro Pro Arg Arg Ser Ser
290 295 300

Ile Arg Asn Ala His Ser Ile His Gln Arg Ser Arg Lys Arg Leu Ser
305 310 315 320

Gln Asp Ala Tyr Arg Arg Asn Ser Val Arg Phe Leu Gln Gln Arg Arg
325 330 335

Arg Gln Ala Arg Pro Gly Pro Gln Ser Pro Gly Ser Pro Leu Glu Glu
340 345 350

Glu Arg Gln Thr Gln Arg Ser Lys Pro Gln Pro Ala Val Pro Pro Arg
355 360 365

Pro Ser Ala Asp Leu Ile Leu Asn Arg Cys Ser Glu Ser Thr Lys Arg
370 375 380

Lys Leu Ala Ser Ala Val
385 390

<210> 19
<211> 2206
<212> DNA
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35 40 45

Ile Leu Lys Asn Met Thr Glu Ala Glu Lys Ala Phe Thr Arg Ser Ile
50 55 60

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Asn Arg Asp Lys His Leu Ala Val Ala Tyr Phe Gln Arg Gly Met Leu
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Tyr Tyr Gln Thr Glu Lys Tyr Asp Leu Ala Ile Lys Asp Leu Lys Glu
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Ala Leu Ile Gln Leu Arg Gly Asn Gln Leu Ile Asp Tyr Lys Ile Leu
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Gly Leu Gln Phe Lys Leu Phe Ala Cys Glu Val Leu Tyr Asn Ile Ala
        115                 120                 125

Phe Met Tyr Ala Lys Lys Glu Glu Trp Lys Lys Ala Glu Glu Gln Leu
    130                 135                 140

Ala Leu Ala Thr Ser Met Lys Ser Glu Pro Arg His Ser Lys Ile Asp
145                 150                 155                 160

Lys Ala Met Glu Cys Val Trp Lys Gln Lys Leu Tyr Glu Pro Val Val
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Ile Pro Val Gly Lys Leu Phe Arg Pro Asn Glu Arg Gln Val Ala Gln
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Leu Ala Lys Lys Asp Tyr Leu Gly Lys Ala Thr Val Val Ala Ser Val
        195                 200                 205

Val Asp Gln Asp Ser Phe Ser Gly Phe Ala Pro Leu Gln Pro Gln Ala
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Ala Glu Pro Pro Pro Arg Pro Lys Thr Pro Glu Ile Phe Arg Ala Leu
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Glu Gly Glu Ala His Arg Val Leu Phe Gly Phe Val Pro Glu Thr Lys
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Glu Glu Leu Gln Val Met Pro Gly Asn Ile Val Phe Val Leu Lys Lys
            260                 265                 270

Gly Asn Asp Asn Trp Ala Thr Val Met Phe Asn Gly Gln Lys Gly Leu
        275                 280                 285

Val Pro Cys Asn Tyr Leu Glu Pro Val Glu Leu Arg Ile His Pro Gln
    290                 295                 300

Gln Gln Pro Gln Glu Glu Ser Ser Pro Gln Ser Asp Ile Pro Ala Pro
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Pro Ser Ser Lys Ala Pro Gly Lys Pro Gln Leu Ser Pro Gly Gln Lys
                325                 330                 335

Gln Lys Glu Glu Pro Lys Glu Val Lys Leu Ser Val Pro Met Pro Tyr
            340                 345                 350

Thr Leu Lys Val His Tyr Lys Tyr Thr Val Val Met Lys Thr Gln Pro
        355                 360                 365

Gly Leu Pro Tyr Ser Gln Val Arg Asp Met Val Ser Lys Lys Leu Glu
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Leu Arg Leu Glu His Thr Lys Leu Ser Tyr Arg Pro Arg Asp Ser Asn
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Glu Leu Val Pro Leu Ser Glu Asp Ser Met Lys Asp Ala Trp Gly Gln
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Val Lys Asn Tyr Cys Leu Thr Leu Trp Cys Glu Asn Thr Val Gly Asp
420 425 430

Gln Gly Phe Pro Asp Glu Pro Lys Glu Ser Glu Lys Ala Asp Ala Asn
435 440 445

Asn Gln Thr Thr Glu Pro Gln Leu Lys Lys Gly Ser Gln Val Glu Ala
450 455 460

Leu Phe Ser Tyr Glu Ala Thr Gln Pro Glu Asp Leu Glu Phe Gln Glu
465 470 475 480

Gly Asp Ile Ile Leu Val Leu Ser Lys Val Asn Glu Glu Trp Leu Glu
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Gly Glu Cys Lys Gly Lys Val Gly Ile Phe Pro Lys Val Phe Val Glu
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Asp Cys Ala Thr Thr Asp Leu Glu Ser Thr Arg Arg Glu Val
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<213> Homo sapiens

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Arg Gly Phe Thr Ser His Phe Val Phe Val Ile Glu Val Lys Thr Lys
35 40 45

Gly Gly Ser Lys Tyr Leu Ile Tyr Arg Arg Tyr Arg Gln Phe His Ala
50 55 60

Leu Gln Ser Lys Leu Glu Glu Arg Phe Gly Pro Asp Ser Lys Ser Ser
65 70 75 80

Ala Leu Ala Cys Thr Leu Pro Thr Leu Pro Ala Lys Val Tyr Val Gly
85 90 95

Val Lys Gln Glu Ile Ala Glu Met Arg Ile Pro Ala Leu Asn Ala Tyr
100 105 110

Met Lys Ser Leu Leu Ser Leu Pro Val Trp Val Leu Met Asp Glu Asp
115 120 125

Val Arg Ile Phe Phe Tyr Gln Ser Pro Tyr Asp Ser Glu Gln Val Pro
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Gln Ala Leu Arg Arg Leu Arg Pro Arg Thr Arg Lys Val Lys Ser Val
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Ser Pro Gln Gly Asn Ser Val Asp Arg Met Ala Ala Pro Arg Ala Glu
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Ala Leu Phe Asp Phe Thr Gly Asn Ser Lys Leu Glu Leu Asn Phe Lys
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Ala Gly Asp Val Ile Phe Leu Leu Ser Arg Ile Asn Lys Asp Trp Leu
195 200 205

Glu Gly Thr Val Arg Gly Ala Thr Gly Ile Phe Pro Leu Ser Phe Val
210 215 220

Lys Ile Leu Lys Asp Phe Pro Glu Glu Asp Asp Pro Thr Asn Trp Leu
225 230 235 240

Arg Cys Tyr Tyr Tyr Glu Asp Thr Ile Ser Thr Ile Lys Ser Val Ala
245 250 255

Trp Glu Gly Gly Ala Cys Pro Ala Phe Leu Pro Ser Leu Arg Pro Pro
260 265 270

Pro Leu Thr Ser Pro Ser His Gly Ser Leu Ser His Ser Lys Ala Pro
275 280 285

Ser Gly Ser Gln Met Ser His Asn Ala Val Thr Ser His Gln Arg Pro
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Gly Trp Pro Gly Gln Pro His Ser Pro Phe Pro His Pro Thr Pro His
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00618

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C12Q 1/26, A61K 31/03, A61K 31/12, A61P 3/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C12Q, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5763496 A (JAMES ARTHUR HOLLAND), 9 June 1998 (09.06.98), column 2, line 4 - line 8; column 10 --	1-26
X	US 5902831 A (JAMES ARTHUR HOLLAND ET AL), 11 May 1999 (11.05.99), column 14"conclusion", column 9 --	1-26
X	Diabetes, Vol. 49, November 2000, Toyoshi Inoguchi et al: "High Glucose Level and Free Fatty Acid Stimulate Reactive Oxygen Species Production Through Protein Kinase C-Dependent Activation of NAD(P)H Oxidase in Cultured Vascular Cells", page 1939 - page 1945, figure 3, page 1940 --	1-26

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2003	22 -07- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carl-Olof Gustafsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00618

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 017533 A1 (HENRY FORD HEALTH SYSTEM), 15 March 2001 (15.03.01), pages 6-8, page 8, lines 1-11, claims --	9,16
A	WO 9912539 A1 (THE JOHNS HOPKINS UNIVERSITY SCHOOL O MEDICINE), 18 March 1999 (18.03.99) --	9,16
A	US 2001019832 A1 (MARGUERITE LUTHMAN), 6 Sept 2001 (06.09.01), examples 1-4, claims -- --------	1-26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/00618

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-25
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/SE03/00618

Claims 9-25 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00618

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5763496 A	09/06/98	AT 189957 T	15/03/00
		AU 1085997 A	19/06/97
		CA 2238098 A,C	05/06/97
		CA 2309881 A	05/06/97
		DE 69606882 D,T	17/08/00
		EP 0861070 A,B	02/09/98
		SE 0861070 T3	
		EP 0914821 A	12/05/99
		ES 2144792 T	16/06/00
		GR 3033067 T	31/08/00
		JP 11507946 T	13/07/99
		US 5902831 A	11/05/99
		WO 9719679 A	05/06/97
US 5902831 A	11/05/99	AT 189957 T	15/03/00
		AU 1085997 A	19/06/97
		CA 2238098 A,C	05/06/97
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		EP 0861070 A,B	02/09/98
		SE 0861070 T3	
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		JP 11507946 T	13/07/99
		US 5763496 A	09/06/98
		WO 9719679 A	05/06/97
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